

## REMARKS

### **I. Status of the Claims**

Claims 1, 3-6 and 8-13 are pending in the application. In response to the restriction requirement which the examiner imposed, applicants elected Group II, claims 3-5 and 10. Thus, claims 1, 6, 8, 9 and 11-13 stand withdrawn. Claims 3-5 and 10 stand rejected, variously, under 35 U.S.C. §112, second paragraph, 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

### **II. Rejection Under 35 U.S.C. §112, Second Paragraph**

Claim 5 is rejected under the second paragraph of §112 as indefinite. Applicants have amended the claim to address the examiner's concerns. Therefore reconsideration and withdrawal of the rejection is respectfully requested.

### **III. Rejection Under 35 U.S.C. §102**

Claims 4 and 10 are rejected as anticipated by Blankenberg *et al.* In so doing, the examiner has cited the Abstract and the Brief Summary of the Invention on pages 2-3 (*i.e.*, paragraphs [0028]-[0035]) with particular reference to paragraphs [0034] and paragraph [0031] as being allegedly anticipatory. Applicants traverse.

#### **A. The Abstract**

The examiner alleges that Blankenberg *et al.* teaches a method of preventing plaque rupture comprising administering Annexin V, by reference to the abstract and Brief Summary of the Invention on pages 2-3. The Abstract states that:

The present invention relies on the affinity of stressed or apoptotic cells for exogenously administered annexin V to create a multi-functional molecular probe that can be simultaneously used for imaging (localization of unstable plaque within the body) and therapy (treatment of unstable plaque).

The abstract specifically refers to the use of a “multi-functional molecular probe” that is created using annexin V, *but not Annexin V itself*, for treatment of unstable plaques. What, then, is the reader to understand the term “multi-functional probe” in the abstract to mean?

Turning to paragraph [0032] of Blankenberg *et al.*, this becomes clear:

[0032] In particular, compositions according to the present invention for detecting and treating vulnerable plaque comprise a binding molecule, a targeting molecule, and an effector molecule. The binding molecule will specifically bind to marker(s) on stressed or apoptotic cells which are characteristic of vulnerable plaque. The targeting molecule will permit localization of the composition when the composition is intravascularly bound to vulnerable plaque. Finally, the effector molecule will selectively kill or inhibit the stressed or apoptotic cells associated with vulnerable plaque. In a first specific embodiment, the binding molecule comprises annexin. In a second specific embodiment, the targeting molecule comprises a radiolabel such as technetium-99m. In a third specific embodiment, the effector molecule comprises a photodynamic agent such as a porphyrin”.

Thus, the reader of Blankenberg *et al.* understands that the reference, in the Abstract, to a “multi-functional molecular probe” is reference to a multi-component complex that comprises: (a) a binding molecule, such as an annexin protein, to allow for specific binding of the “multi-functional molecular probe” to the apoptotic cells of vulnerable plaques; (b) a targeting molecule, such as technetium-99m, to allow localization of the “multi-functional molecular probe” after its administration; and (c) an effector molecule, such a photodynamic agent like porphyrin, to allow the “multi-functional molecular probe” to be activated in order to kill or inhibit the stressed or apoptotic cells following activation.

Thus, the teaching of the utility of Annexin V in the context of atherosclerotic plaques in Blankenberg *et al.* is that it is useful as a ***binding molecule***, and that it can be joined with other so-called ‘localisation’ and ‘effector’ molecules to create a multi-functional complex. It is the multi-functional complex, not Annexin V itself, which is said to be useful for treatment of unstable plaques. Moreover, this utility is explicitly taught by Blankenberg *et al.* to be dependent on the activity of the ‘effector molecules’, ***not Annexin V***, in order to kill apoptotic cells in atherosclerotic plaques. There is no teaching or suggestion in the abstract or elsewhere in Blankenberg *et al.* that Annexin V itself will be useful for preventing atherosclerotic plaque rupture.

This reading of the document is entirely consistent with paragraph [0028] which teaches that “The present invention relies on the affinity of stressed or apoptotic cells for exogenously administered annexin V to create a multi-functional molecular probe ....” Also, paragraph [0029] states that “In a first embodiment, annexin V is labeled with both a radioisotope such as technetium-99m and a photodynamic agent such as a light absorbing porphyrin.” Likewise, paragraph [0030] teaches that “Conversely, annexin V could be conjugated with antisense-DNA or RNA oligonucleotides with a label bond that would lyse upon entry into the target cell trapping the oligonucleotide(s) of interest within.” In all these cases it is clear that Annexin V is only envisaged to be useful as a binding molecule and is not taught to have any capability itself to preventing atherosclerotic plaque rupture.

#### **B. Paragraphs [0031] and [0034]**

As the examiner has given particular emphasis to the teachings of paragraphs [0034] and [0031] of Blankenberg, these are discussed individually below.

The examiner alleges that paragraph [0034] of Blankenberg *et al.* teaches treating a subject exhibiting vulnerable plaques and further alleges that this reads onto preventing plaque rupture in the subject. Paragraph [0034] of Blankenberg *et al.* states:

[0034] Methods according to the present invention for detecting and treating vulnerable plaque comprise administering a composition to a patient suspected of having vulnerable plaque. The composition is capable of specifically binding to the vulnerable plaque, being localized when bound (i.e., detected), and killing or inhibiting the apoptotic or stressed cells characteristic of vulnerable plaque. The methods further comprise determining whether the composition has localized. If the composition has localized, the plaque is determined to be unstable and the patient will be diagnosed as suffering from vulnerable plaque. The treating physician will then activate the composition to kill or inhibit the apoptotic or stressed cells. Usually, the composition will comprise an effector molecule, such as a photodynamic agent such as porphyrin, as described above. Activation will then comprise exposing the localized composition to light in order to activate the photodynamic agent.

The following points are relevant in light of paragraph [0034]. First, paragraph [0034] does not mention annexin proteins at all, much less the specific protein Annexin V in particular. So, paragraph [0034] is clearly not relevant to the novelty of claim 4 when taken in isolation. Second, paragraph [0034] begins with “Methods according to the present invention ....” and so should be interpreted in the context of the earlier disclosures of the application. Moreover, paragraph [0034] goes on to discuss the use of a composition that is “capable of specifically **binding** to the vulnerable plaque, being **localized** when bound (*i.e.*, detected), and **killing** or inhibiting the apoptotic or stressed cells characteristic of vulnerable plaque” (emphasis added). This is clearly a cross-reference to the multi-functional complex of the abstract and paragraph [0032] that is taught to comprise (i) a binding portion (*e.g.*, annexin), (ii) a localization portion (*e.g.*, technetium-99m) and (iii) an effector portion (*e.g.*, porphyrin), as discussed above.

For the reasons given above in respect of the abstract and paragraph [0032], this is clearly **not** a disclosure that ***Annexin V itself*** could or should be used in a method to prevent

atherosclerotic plaque rupture. On the contrary, it is clear from the further disclosure in paragraph [0034] that “the composition will comprise an effector molecule, such as a photodynamic agent such as porphyrin, as described above” that molecules that are ***totally different*** from Annexin V were considered, by the art, to be necessary in order to prevent atherosclerotic plaque rupture. In other words, there is no recognition that Annexin V itself would be capable of preventing atherosclerotic plaque rupture.

The examiner alleges that paragraph [0031] of Blankenberg *et al.* teaches an effective amount of Annexin V to be administered for therapeutic purpose. Paragraph 31 of Blankenberg *et al.*, as relied on by the examiner, states that “[0031] The intrinsic anti-apoptotic properties of internalised Annexin V could also be exploited whereby radiolabeled annexin V for imaging could be co-injected with much greater amounts of unlabeled annexin V ***for therapeutic effect***” (emphasis added). What sort of “therapeutic effect” can be achieved by unlabelled Annexin V? The earlier part of the paragraph alludes to an anti-apoptotic effect. However, it is not at all clear from the contents of paragraph [0031] of Blankenberg that this is disclosure of a “therapeutic effect” ***specifically in respect of atherosclerotic plaques***, as required by claim 4 of the present application. Rather, paragraph [0031] of Blankenberg *et al.* merely discloses that unlabelled Annexin V can be used generally in therapy where an “anti-apoptotic” effect is desired. This is not a disclosure of a method of using Annexin V itself to prevent plaque rupture.

The only specific disclosure in Blankenberg *et al.* of the treatment of vulnerable atherosclerotic plaques is in respect of the use a “multi-functional complex” of (i) a binding molecule such as an annexin protein, (ii) a radioisotope and (iii) an effector molecule to selectively kill or inactivate apoptotic cells in an atherosclerotic plaque. See Blankenberg *et al.*,

paragraph [0032] (as quoted above). In that context, Annexin V is taught *to be useful as a binding molecule* and is not disclosed to have any ability to treat unstable plaques.

Nor is it possible to derive from Blankenberg *et al.* that the anti-apoptotic effect provided by Annexin V, as discussed in paragraph [0031] could be therapeutically beneficial in the prevention of plaque rupture. On the contrary, on closer consideration it can be seen that Blankenberg actually suggests that an anti-apoptotic effect in the cells of an atherosclerotic plaque would *not* be therapeutically beneficial in the prevention of plaque rupture. As discussed above, paragraph [0032] of Blankenberg *et al.* teaches that its multi-functional complexes can be used for “treating vulnerable plaques” via the activity of the effector molecule portion of the complex which “will selectively *kill or inhibit* the stressed or apoptotic cells associated with the vulnerable plaque” (emphasis added).

In view of the foregoing disclosures in Blankenberg *et al.*, the following conclusions can be drawn. First, paragraph [0032] of Blankenberg *et al.* teaches that, in order to treat vulnerable plaques, one should *selectively kill* cells therein, using the disclosed multi-functional complex. Second, paragraph [0031] of Blankenberg *et al.* teaches that unlabelled Annexin V may be useful for exerting *anti-apoptotic effects*. Apoptosis is a form of cell death, and so an anti-apoptotic effect is an effect that *prevents* cell death. The selective killing or inactivation of cells in an atherosclerotic plaque is *the opposite* of preserving such cells by preventing apoptosis. Accordingly, the disclosure in paragraph [0031] of Blankenberg *et al.*, which refers to using “the intrinsic anti-apoptotic effects” of Annexin V for an unspecified “therapeutic effect” clearly cannot be taken to be a teaching that one should use Annexin V itself to prevent the rupture of atherosclerotic plaques. On the contrary, from the disclosure in paragraph [0032], the skilled person would understand that *the opposite effect, i.e., cell killing*, is required to treat vulnerable

plaques. Thus, paragraph [0031] of Blankenberg *et al.* is not a disclosure that Annexin V itself should, or even could, be used to prevent the atherosclerotic plaque rupture.

Of course, in contrast to all of the preceding disclosures, the present application clearly indicates that Annexin V can, by itself, effect protection from plaque rupture. For all of the foregoing reasons, applicants submit that claims 4 and 10 are not anticipated by Blankenberg *et al.* Reconsideration and withdrawal of the rejection are therefore respectfully requested.

#### IV. Rejection Under 35 U.S.C. §103

##### A. Claims 4 and 10

Though claims 4 and 10 are not rejected separately, applicants wish to comment on this issue as the examiner's view in the previous action might also be inferred to take such a position. As discussed above, Blankenberg *et al.* suggests that Annexin V can bind to apoptotic and stressed cells in vulnerable atherosclerotic plaques and so can be used as the 'binding molecule' in a multi-functional probe to cause binding of the probe to those plaques. See the Abstract and paragraphs [0028-0030] and [0032]. Blankenberg *et al.* also suggests that unlabelled annexin V can provide unspecified anti-apoptotic therapeutic effects. See Blankenberg, paragraph [0031]. However, there is no suggestion in Blankenberg *et al.* that such binding or anti-apoptotic effects by Annexin V itself would prevent plaque rupture.

In fact, the overall teaching in Blankenberg *et al.* is that it is necessary to *kill* cells in vulnerable atherosclerotic plaques in order to treat those plaques. See Blankenberg *et al.*, paragraph [0032]. The killing of cells is clearly the *direct opposite* of preservative consequences that would be expected to follow from the anti-apoptotic effects that are taught by Blankenberg *et al.* to be associated with unlabelled Annexin V. See Blankenberg *et al.*, paragraph [0031].

Therefore, the skilled person would understand, from the overall teaching of Blankenberg *et al.*, that although Annexin V may be suitable as a binding molecule for atherosclerotic plaques, if used alone it would be likely to exert an effect that is *opposite* from the effect that is said to be useful for treatment of unstable plaques. As a consequence, the skilled person would not be motivated to try, and would be surprised to discover, that the unlabelled Annexin V protein itself could be used to prevent the rupture of atherosclerotic plaques.

Accordingly, it is clear that the methods of claims 4 and 10 are also non-obvious in light of Blankenberg *et al.*

#### **B. Claims 3-5**

Claims 3-5 are rejected as rendered obvious by Blankenberg *et al.* in view of Manzi *et al.* Once again, applicants traverse.

The examiner alleges that Manzi *et al.* teaches that SLE patients are known to have a greater risk of plaque rupture. However, Manzi *et al.* does not (nor was it cited to) supplement the deficiencies in the teaching of Blankenberg *et al.* Manzi *et al.* says nothing about a potential role for Annexin V in modulating plaque rupture; nor does it suggest that apoptosis should be prevented in order to prevent plaque rupture.

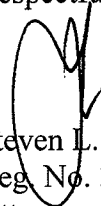
Thus, even if the reader of Blankenberg *et al.* did take into account the teachings of Manzi *et al.*, they would still not be motivated to use Annexin V to prevent atherosclerotic plaque rupture in any patient, much less in an SLE patient. On the contrary, the skilled person would have continued to use the multi-functional complex of Blankenberg *et al.* that utilizes an entirely different molecule as an 'effector molecule' in order to kill the cells of the plaque. In essence, Manzi *et al.* fails to overcome the shortcomings of Blankenberg *et al.*, as outline above.

Accordingly the subject matter of Claims 3-5 and 10 is non-obvious, even in view of the combination of Blankenberg *et al.* and Manzi *et al.* Reconsideration and withdrawal of the rejection is therefore respectfully requested.

**V. Conclusion**

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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